elf atochem
ATO

Elf Atochem North America, Inc.
2000 Market Street
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Tel.: 215.419.7000

8EHQ-1196-13726

November 11, 1996

UPS NEXT DAY DELIVERY

Document Control Office (7407)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M St., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator

8E 13726

Subject: TSCA Section 8(e) Submission

Dear Sir/Madam:

Elf Atochem North America, Inc. (Elf Atochem) has received the final reports of skin and eye irritation studies in rabbits and is submitting these reports to the Environmental Protection Agency (EPA) pursuant to Toxic Substances Control Act (TSCA) Section 8(e). Preliminary results from these studies were submitted to the Agency by Elf Atochem on August 23, 1996. These studies provide information on succinic acid peroxide (CAS Registry Number 123-23-9) and do not involve effects in humans.

Nothing in this letter or the enclosed study reports are considered confidential business information of Elf Atochem.

It is the opinion of Elf Atochem that the effects noted in this study do not necessarily support a conclusion of substantial health risk, but are being submitted in response to the EPA 8(e) reporting standards.

Further questions regarding this submission may be directed to me at (215) 419-5890.

Best Regards,

Debra Randall

Debra Randall, DABT
Product Safety Manager

CONTAINS NO CBI
Date
Per Name Office

A PRIMARY EYE IRRITATION STUDY IN RABBITS WITH SUCCINIC ACID PEROXIDE

CAS Registry Number 123-23-9

AMENDED FINAL REPORT

Author

Deborah A. Douds, M.S.

Original Study Completion Date

August 19, 1996

Amended Study Completion Date

August 29, 1996

Performing Laboratory

Springborn Laboratories, Inc. (SLI)
Health and Environmental Sciences
640 North Elizabeth Street
Spencerville, Ohio 45887

SLI Study No.

3255.100

Submitted to

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103

COMPLIANCE STATEMENT

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58), the EPA (40 CFR Part 792) and the OECD [Annex 2 C(81)30].

Deborah A. Douds

Date 8/19/96

Deborah A. Douds, M.S.
Study Director/Author
Springborn Laboratories, Inc.

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the Study Director in accordance with SLI's Standard Operating Procedures as follows:

Phase	Date
Ocular Observations	06/27/96
Data Audit	08/05/95
Draft Report Review	08/06/96
Final Report Review	08/19/96
Amended Final Report Review	08/29/96
Reports to Study Director and Management	08/06/96, 08/19/96, 08/29/96

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58), the EPA (40 CFR Part 792) and the OECD [Annex 2 C(81)30].

Stephanie J. Schulte Date 8/29/96
Stephanie J. Schulte, B.S.
Quality Assurance Auditor I

Anita M Bosau Date 8/29/96
Anita M. Bosau
Director of Compliance Assurance

The following revised page has been incorporated into this report.

Page No.	Revision	Reason for Change
7	Change the first sentence of the second paragraph under B. Test Article to read as follows: "The test article was stored refrigerated."	As per the label, the test article should have been stored frozen; however, refrigeration of the test article did not have any adverse effect on the test article as per the Sponsor.

Issue of the Report Amendment:

Deborah A Douds Date 8/29/96
Deborah A. Douds, M.S., Study Director

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Appendices

SUMMARY

The potential irritant and/or corrosive effects of Succinic Acid Peroxide were evaluated on the eyes of New Zealand White rabbits. One rabbit received a 0.1000 g (0.1 mL weight equivalent) dose of the test article in the conjunctival sac of the right eye. The contralateral eye of the animal remained untreated and served as a control. The test and control eye was examined for signs of irritation for up to 72 hours following dosing. Due to the amount of irritation noted in the initial rabbit, the remaining animals were not dosed.

Exposure to the test article produced corneal opacity in the test eye at the 1 hour scoring interval. The corneal injury was confirmed by positive fluorescein dye retention at the 24 hour scoring interval. Iritis was observed in the test eye at the 1 hour scoring interval. Conjunctivitis (redness and swelling) was noted in the test eye at the 1 hour scoring interval. Additional ocular findings of blanching of nictating membrane, blanching of conjunctival tissue, ocular discharge-yellow and head tilt were noted in the test eye. Due to the severe irritation noted, the animal was euthanized following the 72 hour score.

Based on the initial rabbit dosed, Succinic Acid Peroxide is considered to be a corrosive to the ocular tissue of the rabbit.

I. INTRODUCTION

This study was performed to assess the irritant and/or corrosive effects of Succinic Acid Peroxide in New Zealand White rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article. This study was performed at Springborn Laboratories, Inc., 553 North Broadway, Spencerville, Ohio. The protocol was signed by the Study Director on June 7, 1996 (GLP initiation date). The in-life phase of the study was initiated with test article administration on June 24, 1996 (day 0) and concluded with final scoring on June 27, 1996.

II. MATERIALS AND METHODS

A. Experimental Protocol

The protocol is included in Appendix A.

B. Test Article

The test article was received from the Sponsor and identified as follows:

Sponsor's ID	Assigned SLI ID	Physical Description	Receipt Date	Expiration Date
Succinic Acid Peroxide Lot No.: 0998603612	S96.012.3255	White solid	May 21, 1996	August 5, 1996

The test article was stored refrigerated. The Sponsor is responsible for any necessary evaluations related to the identity, strength, purity, composition, stability and method of synthesis of the test material according to 21 CFR 58.105, 40 CFR 160.105 and 40 CFR 792.105.

Note: As per the label, the test article should have been stored frozen; however, refrigeration of the test article did not have any adverse effect on the test article as per the Sponsor.

C. Retention Sample

Where necessary, the Sponsor was responsible for maintaining a retention sample of the test article.

D. Test Article Disposition

The remaining test article was returned to the Sponsor following completion of all studies with the test article.

E. Method of Test Article Preparation

The test article was administered as received from the Sponsor.

F. Animals and Animal Husbandry

1. Description, Identification and Housing

Adult, New Zealand White rabbits were received at SLI from Myrtle's Rabbitry, Thompson Station, TN. Upon receipt, plastic ear tags displaying unique identification numbers were used to individually identify the animals. Cage cards displaying at least the study number, animal number and sex were affixed to each cage. The animals were housed individually in suspended stainless steel cages. All housing and care were based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

2. Environment

The animal room temperature and relative humidity ranges were 67-68°F and 62-85%, respectively. The animal room relative humidity range during this study exceeded the preferred range (40-70%) but did not affect the study outcome. Environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers were set to maintain a 12-hour light/12-hour dark cycle and room ventilation was set to produce 10-15 air changes/hour. The animal room temperature and relative humidity were recorded a minimum of once daily.

3. Food

PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.) was provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study were recorded. The feed was analyzed and certified by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits,

contaminants which may have been present were not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These are maintained by SLI.

4. Water

Municipal tap water treated by reverse osmosis was available ad libitum throughout the study. The purified water was supplied by an automatic watering system. Monitoring of the drinking water for contaminants is conducted annually by SLI and the records are available for inspection. Within generally accepted limits, contaminants which may have been present were not expected to compromise the purpose of this study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR, Part 141).

5. Acclimation

Upon receipt, the animals were removed randomly from the shipping cartons, examined by qualified personnel, identified with plastic ear tags and then acclimated to the laboratory conditions for a minimum of five days. The animals were observed daily for overt physical or behavioral abnormalities, general health/moribundity and mortality.

6. Animal Selection

The animals chosen for study use were arbitrarily selected from healthy stock animals to avoid potential bias. All animals received a detailed pretest observation prior to dosing. Only healthy animals were chosen for study use. Females were nulliparous and nonpregnant.

III. EXPERIMENTAL PROCEDURES

A. Preliminary Examination

On day 0 prior to dosing, both eyes of each animal provisionally selected for test use were examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface was examined using fluorescein sodium dye. One drop of a fluorescein/physiological saline mixture was gently dropped onto the superior sclera of each eye. Following an approximate 15 second exposure, the eyes were thoroughly rinsed with physiological saline. The corneal surface was then examined for dye retention under a long-wave UV light source. Animals exhibiting

ocular irritation, preexisting corneal injury or fluorescein dye retention were not used on study. All animals found to be acceptable for test use were returned to their cages until dosing.

B. Dosing

A minimum of one hour after preliminary ocular examination, the test article was instilled as follows:

Group	Concentration (%)	Amount Instilled	No. of Animals Females
No Rinse	100	0.1000 g	1

The test article was instilled into the conjunctival sac of the right eye of the animal after gently pulling the lower lid away from the eye. Following instillation, the eyelids were gently held together for approximately one second in order to limit test article loss and the animal was returned to its cage. The contralateral eye remained untreated to serve as a control.

C. Ocular Observations

The eyes were macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours after dosing according to the Ocular Grading System presented in Protocol Appendix A which is based on Draize [2]. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure was repeated on all test and control eyes and any residual test article was gently rinsed from the eye at this time (if possible) using physiological saline. If any fluorescein findings were noted at 24 hours, a fluorescein exam was conducted on the affected eyes at each subsequent interval until a negative response was obtained or as directed by the Study Director.

D. Clinical Observations

Any unusual observations and/or mortality were recorded. General health/mortality checks were performed twice daily (in the morning and in the afternoon).

E. Body Weights

Body weight was obtained for the animal prior to dosing on day 0.

F. Gross Necropsy

The animal was euthanized by an intravenous injection of sodium pentobarbital following its final observation interval. Gross necropsy examinations were not required for this animal.

G. Protocol Deviations

No protocol deviations occurred during this study.

IV. ANALYSIS OF DATA

The ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) was multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each interval.

The data will be analyzed and summarized in the report based on the definitions presented below:

1. Non Irritant - Following instillation of the test article, none of the test eyes showed a positive effect as defined in the Ocular Grading System in Protocol Appendix A.

2. Irritant - Following instillation of the test article, one or more test eyes exhibited a positive effect, but the changes were reversible.

3. Corrosive - One or more test eyes exhibited irreversible changes (ex., necrosis or ulceration) following instillation of the test article.

V. MAINTENANCE OF RAW DATA AND RECORDS

All original paper data, the final report and magnetically encoded records were transferred to the SLI archives for a period of 10 years. The Sponsor will be contacted prior to final disposition of these items.

VI. RESULTS

A. Ocular Observations:

Individual Data: Table 1

Exposure to the test article produced corneal opacity in the test eye at the 1 hour scoring interval. The corneal injury was confirmed by positive fluorescein dye retention at the 24 hour scoring interval. Iritis was observed in the test eye at the 1 hour scoring interval. Conjunctivitis (redness and swelling) was noted in the test eye at the 1 hour scoring interval. Additional ocular findings of blanching of nictating membrane, blanching of conjunctival tissue, ocular discharge-yellow and head tilt were noted in the test eye. Due to the severe irritation noted, the animal was euthanized following the 72 hour score.

No corneal opacity, iritis or conjunctivitis was observed in the control eyes.

VII. CONCLUSION

Based on the initial rabbit dosed, Succinic Acid Peroxide is considered to be a corrosive to the ocular tissue of the rabbit.

Deborah A. Douds

Date 8/19/96

Deborah A. Douds, M.S.
Study Director

VIII. REPORT REVIEW

Todd N. Merriman

Date 8/19/96

Todd N. Merriman, B.S., LATG
Toxicologist

Kimberly L. Bonnette

Date 8/19/96

Kimberly L. Bonnette, M.S., LATG
Manager of Acute Toxicology

IX. REFERENCES

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.

2. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

SLI STUDY NO.: 3255.100
CLIENT: ELF ATOCHEM

TABLE 1
A PRIMARY EYE IRRITATION STUDY IN RABBITS
INDIVIDUAL OCULAR IRRITATION SCORES
(NO RINSE GROUP)

Animal No./Sex	Scoring	Cornea			Iris		Conjunctivae					Test Eye[a]		Control Eye[a]	
Body Weight (kg)	Interval	O	A	OxAx5	I	Ix5	R	S	D	(R+S+D)2	Total	Fluorescein Examination	Secondary Ocular Findings	Fluorescein Examination	Secondary Ocular Findings
4008/F	1 Hour	4	4	80	1	5	2	2	0	8	93		BNB, BCT[a]		
2.986	24 Hours	4	4	80	1	5	2	2	0	8	93	FAO	BNB, BCT	[-]	
	48 Hours	4	4	80	[b]	-	2	3	2	14	94	FAO	BNB, BCT, ODY[c]		
	72 Hours	4	4	80	[b]	-	2	3	3	16	96	FAO	BNB, BCT, ODY[c]		

[a]See Protocol Appendix A for definition of codes.
[a]Animal does not appear to be in any pain/distress.
[b]Cannot be determined due to degree of opacity.
[c]Animal still appears to be eating and is in good health.

BNB = Blanching of nictating membrane; BCT = Blanching of conjunctival tissue; ODY = Ocular discharge - yellow.

APPENDIX A

Protocol

A PRIMARY EYE IRRITATION STUDY IN RABBITS WITH SUCCINIC ACID PEROXIDE

PROTOCOL

Springborn Study No. 3255.100

Protocol No.: ELFATO/EI-1
Issue Date: February 1996

Springborn Laboratories, Inc. (SLI)
Health and Environmental Sciences
640 North Elizabeth Street
Spencerville, Ohio 45887

Deborah A. Douds, M.S.
Study Director

For

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103

TABLE OF CONTENTS

I. PURPOSE

The purpose of this study is to assess the irritant and/or corrosive effects of a test article in rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article.

II. RESPONSIBILITIES

A. Sponsor

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103

B. Sponsor's Representative

Roy Bannister, Ph.D.
Phone: (215) 419-5875
FAX: (215) 419-5800

C. Testing Location

Springborn Laboratories, Inc.
Health and Environmental Sciences
553 North Broadway
Spencerville, OH 45887
Phone: (419) 647-4196
FAX: (419) 647-6560

D. Personnel Responsibilities

1. Deborah A. Douds, M.S.
   Study Director/Toxicologist

2. Kimberly L. Bonnette, M.S., LATG
   Alternate Contact/Manager of Acute Toxicology

3. Todd N. Merriman, B.S., LATG
   Toxicologist

4. Robert B. Foster
   President and Managing Director

5. Malcolm Blair, Ph.D.
   Director of Research

6. Rusty E. Rush, M.S., LAT, DABT
   Associate Director of Toxicology

7. J. Dale Thurman, D.V.M, M.S., DACVP
   Director of Pathology

8. Elaine Daniel, Ph.D., DABT
   Associate Director of Toxicology

9. Anita M. Bosau
   Director of Compliance Assurance

III. PROPOSED STUDY SCHEDULE

A. Initiation of In-Life Phase: June, 1996

B. Completion of In-Life Phase: July, 1996

C. Audited Report Date: 4 Weeks Following Sponsor's Approval for Study Termination

IV. TEST ARTICLE IDENTIFICATION

A. Test Article

1. Sponsor's Identification

Succinic Acid Peroxide

2. SLI Test Article Identification Number

S96.012.3255

3. Characteristics

The Sponsor is responsible for any necessary evaluations related to identity, strength, purity, composition, stability and method of synthesis of the test material according to 21 CFR 58.105 and 40 CFR 792.105. Any special storage conditions for the test article will be supplied by the Sponsor.

4. Handling Precautions

Safety data regarding the test article should be provided by the Sponsor [Material Safety Data Sheet (MSDS), if available]. Technical personnel are required to read this information prior to handling the test article. Any question concerning this information should be referred to the Study Director.

Additional safety and handling information may be provided by the Study Director and/or Sponsor. Minimum safety requirements include safety glasses, impervious gloves, and laboratory wear. An MSDS shall also be available for any other chemical entities utilized in the conduct of this study.

B. Retention Sample

Where necessary, the Sponsor will be responsible for maintaining a retention sample of the test article.

C. Test Article Disposition

The test article will be returned to the Sponsor following completion of all studies with the test article(s) unless otherwise instructed by the Sponsor.

D. Method of Test Article Preparation

Liquids, gels and pastes are generally administered as received from the Sponsor. Solids and powders are generally ground and sieved prior to test use. This may be accomplished by grinding the material in a mortar and pestle and passing the material through a No. 40 mesh sieve. The weight of processed test article that occupies a volume of 0.1 mL will be determined by measuring a convenient volume (at least 2 mL) of the powder in a suitable volumetric container. The powder will be gently compacted by tapping the measuring container. The test article dose per eye will then be calculated (weight equivalent of 0.1 mL, not to exceed 0.1 g). The test article will be prepared and/or dispensed fresh on the day of dosing. The method of preparation will be documented in the raw data and presented in the final report.

V. TEST SYSTEM

A. Justification of the Test System

1. The rabbit is the preferred species for primary eye irritation testing by various U.S. and International regulatory agencies.

2. The New Zealand White rabbit has been shown to be sensitive to the irritant/corrosive effects of a variety of drugs and chemicals. Therefore, this species and strain is a reasonable alternative to larger mammals for primary eye irritation testing of drugs and chemicals for human safety assessment.

3. The New Zealand White rabbit has been used extensively for eye irritation testing. Thus, data from this study may be compared and contrasted to other studies performed in New Zealand White rabbits.

4. Historical information concerning New Zealand White rabbits is available at SLI and in the published literature.

5. Healthy, outbred New Zealand White rabbits may be obtained from reliable, USDA approved and regulated suppliers.

6. The laboratory rabbit may be safely handled and manipulated by trained technical personnel.

SLI has conducted literature searches through Medline, Toxline and Bioethics and there are no generally accepted validated alternatives to this test. In a 1989 position paper prepared by the Animals in Research Committee of The Society of Toxicology (SOT) and approved by the SOT Council, it was concluded that "none of these proposed models are yet validated or evaluated for a broad range of chemical moieties, and none can be relied upon to provide the scientific reliability or predictive accuracy which would be required for a new test for regulatory of legal acceptability" [1].

B. Justification of the Route of Exposure and Number of Animals

1. Ocular administration of the test substance was selected since this is a potential route of human exposure.

2. Since New Zealand White rabbits have no pigment and have an easily accessible ocular area, substances may be accurately instilled and any resulting effects easily observed.

3. The number of animals used on this study will be consistent with the guidelines published by a number of U.S. and International regulatory agencies including EPA-FIFRA, EPA-TSCA, FDA, CPSC-FHSA, DOT, IMO, EEC, OECD, MAFF and MOHW.

C. Description

1. Species

Rabbit

2. Strain

New Zealand White

3. Source

Myrtle's Rabbitry or another USDA approved supplier

4. Age and Body Weight Range

Adult, approximately 2.0 to 3.5 kg (prior to dosing on day 0).

5. Number of Animals/Sex on Study

6 rabbit test (males and/or females)

D. Method of Identification

Plastic ear tags displaying unique identification numbers will be used to individually identify the animals. The cage cards will display at least the study number, animal number, and sex and will be affixed to each cage.

E. Animal Husbandry

1. Housing

The animals will be housed individually in suspended stainless steel cages. All housing and care will be based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [2].

2. Environment

The environmental conditions for the animal room will be set to maintain room temperature and relative humidity ranges of 67 ± 6°F and 55 ± 15%, respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers will be set to maintain a 12-hour light/12-hour dark cycle and the room ventilation will be set to produce 10-15 air changes/hour. The room temperature and relative humidity will be recorded a minimum of once daily.

3. Food

PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.) will be provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study will be recorded. The feed is analyzed and certified by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, there are no contaminants reasonably expected in the diet which would interfere with the conduct of the study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained in the laboratory records. Feed that is outside the ranges set for the above mentioned criteria will not be utilized by the testing facility.

4. Water

Municipal tap water following treatment by reverse osmosis will be available ad libitum throughout the study. The purified water will be supplied by an automatic watering system. Monitoring of the drinking water for contaminants will be conducted annually by the testing laboratory and the records will be available for inspection. Levels of contaminants which may be present are not expected to compromise the purpose of the study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR, Part 141).

F. Acclimation

Upon receipt, the animals will be removed randomly from the shipping cartons, examined by qualified personnel, identified with plastic ear tags, and then acclimated to the laboratory conditions for a minimum of 5 days. The animals will be observed daily for overt physical or behavioral abnormalities, general health/moribundity and mortality.

G. Animal Selection

The animals chosen for study use will be arbitrarily selected from healthy stock animals to avoid potential bias. All animals will receive a detailed pretest observation prior to dosing. Only healthy animals will be chosen for study use. Females will be nulliparous and nonpregnant.

VI. EXPERIMENTAL DESIGN AND PROCEDURES

A. Study Group Design

A six rabbit test will be performed. Materials which are determined by the Sponsor to be strong acids (pH ≤ 2.0), strong alkalis (pH ≥ 11.5) or a material which produces severe dermal irritation need not be tested in a full number of animals due to their predictive corrosive properties. However, at the request of the Sponsor, these materials will be administered to one animal. If no corrosive response is seen during the first 72 hours, the material will be tested on the remaining five animals.

B. Preliminary Examination

On day 0 prior to dosing, both eyes of each animal provisionally selected for test use will be examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface will be examined using fluorescein sodium dye. One drop of a fluorescein/physiological saline mixture will be gently dropped onto the superior sclera of each eye. Following an approximate 15 second exposure, the eyes will be rinsed with physiological saline. The corneal surface will then be examined for dye retention under a long-wave UV light source. Animals exhibiting ocular irritation, preexisting corneal injury or fluorescein dye retention will not be used on study. All animals found to be acceptable for test use will be returned to their cages until dosing.

C. Dosing

A minimum of one hour after preliminary ocular examination, the test article will be instilled into the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eye. Liquids, gels and pastes will be administered at a volume of 0.1 mL. Solids and powders will be administered at a weight equivalent to 0.1 mL volume, not to exceed 0.1 g. Following instillation, the eyelids will be gently held together for approximately one second in order to limit test article loss and the animal returned to its cage. The contralateral eye will remain untreated to serve as a control. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If such is noted, the Sponsor will be contacted to see if the animals should be humanely euthanized.

D. Body Weights

Individual body weights will be obtained for each animal prior to dosing on day 0.

E. Ocular Observations

The eyes will be macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours after dosing according to the Ocular Grading System presented in Protocol Appendix A which is based on Draize [3]. At the discretion of the Study Director, a bimicroscopic slit-lamp may be utilized to further examine and clarify ocular lesions. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure will be repeated on all test and control eyes and any residual test article should be gently rinsed from the eye at this time (if possible) using physiological saline. If any fluorescein findings are noted at 24 hours, a fluorescein exam will be conducted on the affected eyes at each subsequent interval until a negative response is obtained or as directed by the Study Director. If there is no evidence of treatment related ocular irritation at the 72 hour scoring interval, the study will be terminated. If ocular irritation persists in any test eye, the observation period may be extended for the affected animals (scored on days 7, 10, 14 and 21). Animals requiring an extended observation period will remain on test (up to and including 21 days post-dose) until the irritation has resolved, permanent injury is evident or the Study Director/Sponsor determines that additional scoring intervals are unnecessary.

F. Clinical Observations

Any unusual observations and mortality will be recorded. General health/mortality checks wili be performed twice daily (in the morning and in the afternoon).

G. Unscheduled Deaths and Euthanasia

Any animals dying or euthanized for cause during the study period will be necropsied. The animals will be euthanized by an intravenous injection of sodium pentobarbital. Body cavities (cranial, thoracic, abdominal and pelvic) will be opened and examined. No tissues will be retained.

H. Scheduled Euthanasia

Each surviving animal will be euthanized by intravenous injection of sodium pentobarbital following its final observation interval. A gross necropsy examination will not be required for surviving animals.

VII. PROTOCOL AMENDMENT

Alterations to this protocol may be made as the study progresses. No changes in the protocol will be made without the specific consent of the Sponsor's Representative. A protocol amendment will be prepared and signed by the Study Director, SLI Quality Assurance and Sponsor's Representative for any such changes.

VIII. DATA REPORTING

One unbound copy of the draft report (if requested) and two copies of the final report (one bound and one unbound) will be submitted to the Sponsor. The final report will include all information necessary to provide a complete and accurate description and evaluation of the experimental procedures and results.

The report will include at least the following information and data:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References
- Data Tables
- Protocol and Amendments
- SLI Personnel Responsibilities

IX. ANALYSIS OF DATA

For each group, the ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) will be multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each animal/interval. The group mean irritation score will then be calculated for each scoring interval based on the number of animals initially dosed in each group. If an animal dies during the study, the total animals in that group will be reduced (by the number of animals dead) for each subsequent scoring interval for the purpose of calculating the mean ocular irritation score for each interval.

The data will be analyzed and summarized in the report based on the definitions presented below:

1. Non Irritant - Following instillation of the test article, none of the test eyes show a positive effect as defined in the Ocular Grading System in Protocol Appendix A.

2. Irritant - Following instillation of the test article, one or more test eyes exhibit a positive effect, but the changes are reversible.

3. Corrosive - One or more test eyes exhibit irreversible changes (ex., necrosis or ulceration) following instillation of the test article.

X. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

All original data, magnetically encoded records, specimens and reports from this study are the property of the Sponsor. These materials shall be available at SLI to facilitate auditing of the study during its progress and prior to acceptance of the final report. All original paper data, the final report, magnetically encoded records, and any specimens will be transferred to the SLI archives for a period of 10 years. The Sponsor will be contacted prior to the final disposition of these items.

XI. REGULATORY COMPLIANCE

This study may be submitted to and will be conducted in accordance with the EPA-TSCA [4], OECD [5], and EEC [6] guidelines and the principles of the Good Laboratory Practice regulations by the FDA (21 CFR Part 58), the EPA (40 CFR Part 792) and the OECD [Annex 2 C(81)30].

XII. QUALITY ASSURANCE

The study will be inspected at least once during the in-life phase by the Springborn Laboratories, Inc., Quality Assurance Unit to assure compliance with Good Laboratory Practice regulations, SLI's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The final report will be audited prior to submission to the Sponsor to ensure that it completely and accurately describes the test procedures and results of the study.

XIII. USDA ANIMAL WELFARE COMPLIANCE STATEMENT

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress and pain to animals. All methods are described in this study protocol or in written laboratory standard operating procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management. Methods of euthanasia used during this study are in conformance with the above referenced regulations and the American Veterinary Medical Association Panel on Euthanasia [7]. This protocol has been reviewed and approved by Springborn Laboratories, Inc. Institutional Animal Care and Use Committee (IACUC) for a maximum of 12 animals. Prior IACUC approval will be obtained for repeated studies.

This study is being conducted to evaluate potential irritant effects of the test article and potential reversibility of such effects. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress post-dose or if delayed severe ocular or clinical changes subsequently develop. If severe reactions are noted, the Study Director will contact the Facility Veterinarian and Sponsor to consider an appropriate course of action. In the event that the Sponsor cannot be contacted, the Study Director and Facility Veterinarian may

authorize treatment or euthanasia of the animals. In general, the ocular tissue will not be anesthetized prior to or following dosing since these substances have been shown to inhibit the blink and/or tear response which may alter the irritation response. Furthermore, anesthetic agents may interact with and/or dilute the test article and thereby alter the experimental results. However, if it is suspected that the test article may induce more than transient pain/distress based on existing information, preanesthesia will be considered. In such circumstances, the Study Director and/or Facility Veterinarian will consult with the Sponsor to devise an appropriate study plan.

XIV. DECLARATION OF INTENT

This study will be listed on the SLI Quality Assurance Master Schedule for the EPA.

XV. GENERIC PROTOCOL APPROVAL

The Sponsor's signature below documents that there are no acceptable non-animal alternatives for this study, and that since this study is required by the relevant supervising government agency, it does not unnecessarily duplicate any previous experiments.

Kimberly L. Bonnette, M.S., LATG
Manager of Acute Toxicology

Date: 3/20/96

Quality Assurance Unit (SLI)

Date: 3/20/96

Roy Bannister, Ph.D.
Sponsor's Representative
(Principal Investigator)

Date: 3/22/96

XVI. STUDY SPECIFIC PROTOCOL APPROVAL

Deborah A. Douds, M.S.
Study Director (SLI)

Date: 6/7/96

Quality Assurance Unit (SLI)

Date: 6/7/96

XVII. REFERENCES

1. SOT Position Paper, "Comments on the LD50 and Acute Eye and Skin Irritation Tests, Fundamental and Applied Toxicology 13, 621-623, 1993.

2. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.

3. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

4. Toxic Substances Control Act Test Guidelines, 40 CFR Part 798, Subpart E, Section 798.4500, July 1, 1992.

5. OECD Guidelines for the Testing of Chemicals, Section 4, Health Effects, Subsection 405, February 24, 1987.

6. The EEC Guidelines Part B: Method for the Determination of Toxicity, No. L 383 A/127, B.5, December 29, 1992.

7. 1993 Report of the American Veterinary Medical Assoc. Panel on Euthanasia, JAVMA, Vol. 202, No. 2, pp. 229-249, January 15, 1993.

PROTOCOL APPENDIX A

Ocular Grading System

(O) CORNEAL OPACITY–DEGREE OF DENSITY (AREA MOST DENSE TAKEN FOR READING)	
OBSERVATION	CODE
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	1*
Easily discernible translucent area, details of iris slightly obscured	2*
Nacreous (opalescent) area, no details of iris visible, size of pupil barely discernible	3*
Opaque cornea, iris not discernible through opacity	4*

(A) AREA OF CORNEA INVOLVED (TOTAL AREA EXHIBITING ANY OPACITY, REGARDLESS OF DEGREE)	
OBSERVATION	CODE
No ulceration or opacity	0
One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

Cornea Score = O x A x 5 Total Maximum = 80

(I) IRITIS	
OBSERVATION	CODE
Normal	0
Markedly deepened rugae (folds above normal), congestion, swelling, moderate circumcorneal hyperemia or injection, any or all of these or combination of any thereof, iris is still reacting to light (sluggish reaction is positive)	1*
No reaction to light, hemorrhage, gross destruction (any or all of these)	2*

Iris Score = I x 5 Total Maximum = 10

*Positive Effect.

PROTOCOL APPENDIX A

Ocular Grading System

(R) CONJUNCTIVAL REDNESS (REFERS TO PALPEBRAL AND BULBAR CONJUNCTIVAE EXCLUDING CORNEA AND IRIS)	
OBSERVATION	CODE
Blood vessels normal	0
Some blood vessels definitely hyperemic (injected) above normal (slight erythema)	1
Diffuse, crimson color, individual vessels not easily discernible (moderate erythema)	2*
Diffuse beefy red (marked erythema)	3*

(S) CONJUNCTIVAL SWELLING (LIDS AND/OR NICTATING MEMBRANE)	
OBSERVATION	CODE
No swelling	0
Any swelling above normal (includes nictitating membrane, slightly swollen)	1
Obvious swelling with partial eversion of lids	2*
Swelling with lids about half closed	3*
Swelling with lids more than half closed	4*

(D) CONJUNCTIVAL DISCHARGE	
OBSERVATION	CODE
No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs and considerable area around the eye	3

Conjunctival Score = (R + S + D) x 2 Total Maximum = 20

*Positive Effect.

PROTOCOL APPENDIX A

Ocular Grading System

CORNEAL NEOVASCULARIZATION		
OBSERVATION	CODE	DEFINITION
Neovascularization - Very Slight	VAS-1	Total area of vascularized corneal tissue is < 10% of corneal surface
Neovascularization - Mild	VAS-2	Total area of vascularized corneal tissue is > 10% but < 25% of corneal surface
Neovascularization - Moderate	VAS-3	Total area of vascularized corneal tissue is > 25% but < 50% of corneal surface
Neovascularization - Severe	VAS-4	Total area of vascularized corneal tissue is > 50% of corneal surface

SECONDARY OCULAR FINDINGS		
OBSERVATION	CODE	DEFINITION
Sloughing of the corneal epithelium	SCE	Corneal epithelial tissue is observed to be peeling off the corneal surface.
Corneal bulging	CB	The entire corneal surface appears to be protruding outward further than normal.
Slight dulling of normal luster of the cornea	SDL	The normal shiny surface of the cornea has a slightly dulled appearance.
Raised area on the corneal surface	RAC	A defined area on the corneal surface that is raised above the rest of the cornea. This area is generally associated with neovascularization and has a off-white to yellow color.
Corneal edema	CE	The cornea has a swollen appearance.
Test article present in eye	TAE	Apparent residual test article is observed on the eye or in the conjunctival sac/inner canthus.
Observation confirmed by slit lamp	OCS	A slit lamp examination was performed to confirm the initial observation.
Corneal mineralization	CM	Small white or off-white crystals that are observed in the corneal tissue.

PROTOCOL APPENDIX A

Ocular Grading System

FLUORESCEIN EXAMINATION OF CORNEA	
OBSERVATION	CODE
Fluorescein Dye Retention Fluorescein dye retention associated with the area of corneal opacity Fluorescein dye retention is not associated with any other finding	 FAO FNF
Negative Results No fluorescein retention is observed	 (-)
Secondary Ocular Findings Superficial mechanical abrasion to the cornea observed during the fluorescein examination period Fine stippling on the cornea observed during the fluorescein examination procedure	 MI ST

POST-DOSE CLINICAL OBSERVATIONS	
OBSERVATION	CODE
Animal vocalized following dosing	VOC
Animal excessively pawed test eye following dosing	PAW
Animal exhibited excessive hyperactivity following dosing	HYP
Animal exhibited excessive head tilt following dosing	HT
Animal exhibited excessive squinting of test eye following dosing	SQ

Any additional findings will be noted in the raw data and in the final report.

APPENDIX B

Individual Clinical Observations

A PRIMARY EYE IRRITATION STUDY IN RABBITS
INDIVIDUAL CLINICAL OBSERVATIONS

Animal No./Sex	Clinical Observation
4008/F	Head tilt; 24, 48 hours

APPENDIX C

SLI Personnel Responsibilities

SLI PERSONNEL RESPONSIBILITIES

Deborah A. Douds, M.S.	Study Director/Toxicologist
Kimberly L. Bonnette, M.S., LATG	Alternate Contact/Manager of Acute Toxicology
Robert B. Foster	President and Managing Director
Malcolm Blair, Ph.D.	Director of Research
Rusty E. Rush, M.S., LAT, DABT	Associate Director of Toxicology
Todd N. Merriman, B.S., LATG	Toxicologist
Patricia K. Jenkins, A.A.S., LATG, RILAM	Supervisor of Acute Toxicology
Pamela S. Smith, ALAT	Unit Leader
Delores P. Knippen	Supervisor of Pharmacy
Jan K. Severt, B.S., ALAT	Supervisor of Acute Report Preparation
Anita M. Bosau	Director of Compliance Assurance
J. Dale Thurman, D.V.M., M.S., DACVP	Director of Pathology

A PRIMARY SKIN IRRITATION STUDY IN RABBITS WITH SUCCINIC ACID PEROXIDE

CAS Registry Number 123-23-9

FINAL REPORT

Author

Deborah A. Douds, M.S.

Study Completed on

August 29, 1996

Performing Laboratory

Springborn Laboratories, Inc. (SLI)
Health and Environmental Sciences
640 North Elizabeth Street
Spencerville, Ohio 45887

SLI Study No.

3255.101

Submitted to

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103

COMPLIANCE STATEMENT

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58), the EPA (40 CFR Part 792) and the OECD [Annex 2 C(81)30].

Deborah A. Douds Date 8/29/96

Deborah A. Douds, M.S.
Study Director/Author
Springborn Laboratories, Inc.

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the Study Director in accordance with SLI's Standard Operating Procedures as follows:

Phase	Date
Dermal Observations	06/07/96
Data Audit	07/10/96
Draft Report Review	07/10/96
Final Report Review	08/29/96
Reports to Study Director and Management	07/10/96, 08/29/96

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58), the EPA (40 CFR Part 792) and the OECD [Annex 2 C(81)30].

Julie D. Perry Date 8/29/96

Julie D. Perry, B.S.
Senior Quality Assurance Auditor

Anita M. Bosau Date 8/29/96

Anita M. Bosau
Director of Compliance Assurance

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Appendices

SUMMARY

The potential irritant and/or corrosive effects of Succinic Acid Peroxide were evaluated on the skin of New Zealand White rabbits. Each of six rabbits received a 0.5 g dose of the test article as a single dermal application. The dose was held in contact with the skin under a semi-occlusive binder for an exposure period of four hours. Following the exposure period, the binder was removed and the remaining test article was wiped from the skin using gauze moistened with distilled water followed by dry gauze. Test sites were subsequently examined and scored for dermal irritation for up to 14 days following patch removal.

Exposure to the test article produced moderate edema and moderate to severe blanching on 6/6 test sites at the 1 hour scoring interval. Additional dermal findings included eschar exfoliation and desquamation which were noted on 4/6 and 5/6 test sites, respectively, and apparent necrosis and eschar which were both noted on 6/6 test sites. The dermal irritation resolved completely in 1/6 animals by study day 14.

Under the conditions of this test, Succinic Acid Peroxide is considered to be a corrosive to the skin of the rabbit.

I. INTRODUCTION

This study was performed to assess the potential irritant and/or corrosive effects of Succinic Acid Peroxide in New Zealand White rabbits when administered by a single dermal dose. This study is intended to provide information on the potential health hazards of the test article with respect to dermal exposure. Data from this study may serve as a basis for classification and/or labeling of the test article. This study was performed at Springborn Laboratories, Inc., 553 North Broadway, Spencerville, Ohio. The protocol was signed by the Study Director on June 4, 1996 (GLP initiation date). The in-life phase of the study was initiated with test article administration on June 5, 1996 and concluded with final scoring on June 19, 1996.

II. MATERIALS AND METHODS

A. Experimental Protocol

The protocol is included in Appendix A.

B. Test Article

The test article was received from the Sponsor and identified as follows:

Sponsor's ID	Assigned SLI ID	Physical Description	Receipt Date	Expiration Date
Succinic Acid Peroxide Lot No.: 0998603612	S96.012.3255	White solid	May 21, 1996	August 5, 1996

The test article was stored refrigerated. The Sponsor is responsible for any necessary evaluations related to identity, strength, purity, composition, stability and method of synthesis of the test material according to 21 CFR 58.105 and 40 CFR 792.105.

Note: As per the label, the test article should have been stored frozen, however, refrigeration of the test article did not have any adverse effect on the test article as per the Sponsor.

C. Retention Sample

Where necessary, the Sponsor was responsible for maintaining a retention sample of the test article.

D. Test Article Disposition

The remaining test article was returned to the Sponsor following completion of all studies with the test article.

E. Method of Test Article Preparation

The test article was administered as received from the Sponsor.

F. Animals and Animal Husbandry

1. Description, Identification and Housing

Adult, New Zealand White rabbits were received at SLI from Myrtle's Rabbitry, Thompson Station, TN. Upon receipt, plastic ear tags displaying unique identification numbers were used to individually identify the animals. Cage cards displaying at least the study number, animal number and sex were affixed to each cage. The animals were housed individually in suspended stainless steel cages. All housing and care were based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

2. Environment

The animal room temperature and relative humidity ranges were 66-71°F and 56-78%, respectively. The relative humidity range during this study exceeded the preferred range (40-70%) but did not affect the study outcome. Environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers were set to maintain a 12-hour light/12-hour dark cycle and room ventilation was set to produce 10-15 air changes/hour. The animal room temperature and relative humidity were recorded a minimum of once daily.

3. Food

PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.) was provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study were recorded. The feed was analyzed and certified by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits,

contaminants which may have been present were not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These are maintained by SLI.

4. Water

Municipal tap water treated by reverse osmosis was available ad libitum throughout the study. The purified water was supplied by an automatic watering system. Monitoring of the drinking water for contaminants is conducted annually by SLI and the records are available for inspection. Within generally accepted limits, contaminants which may have been present were not expected to compromise the purpose of this study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR, Part 141).

5. Acclimation

Upon receipt, the animals were removed randomly from the shipping cartons, examined by qualified personnel, identified with plastic ear tags and then acclimated to the laboratory conditions for a minimum of five days. The animals were observed daily for overt physical or behavioral abnormalities, general health/moribundity and mortality.

6. Animal Selection

The animals chosen for study use were arbitrarily selected from healthy stock animals to avoid potential bias. All animals received a detailed pretest observation prior to dosing. Only healthy animals were chosen for study use.

III. EXPERIMENTAL PROCEDURES

A. Preliminary Procedures

On day -1, the animals chosen for use on the primary skin irritation study had the fur removed from the dorsal area of the trunk using an animal clipper. Care was taken to avoid abrading the skin during the clipping procedure.

B. Dosing

On the following day (day 0), the test article was applied to a small area of intact skin on each test animal (approximately 1 inch x 1 inch) as indicated below:

Concentration (%)	Amount Applied	Patch Design	No. of Animals Males
100	0.5 g	1" x 1" square 4 ply gauze patch	6

The test article was administered to the gauze patch. The test article was then moistened with 0.5 mL of distilled water and the gauze patch applied to the test site. The gauze patch was held in contact with the skin at the cut edges with a nonirritating tape. Removal and ingestion of the test article was prevented by placing an elastic wrap over the trunk and test area (semi-occlusive binding). The elastic wrap was then further secured with adhesive tape around the trunk at the cranial and caudal ends.

After dosing, collars were placed on each animal and remained in place until removal on day 3. After a four-hour exposure period, the elastic wrap and gauze patch were removed from each animal and the corners of the test site delineated using a marker. Residual test article was removed using gauze moistened with distilled water followed by dry gauze.

C. Dermal Observations

Animals were examined for signs of erythema and edema and the responses scored at approximately 1, 24, 48 and 72 hours and up to 14 days after patch removal according to the Macroscopic Dermal Grading System presented in Protocol Appendix A which is based on Draize [2].

D. Clinical Observations

Any unusual observations and/or mortality were recorded. General health/mortality checks were performed twice daily (in the morning and in the afternoon).

E. Body Weights

Individual body weights were obtained for each animal prior to dosing on day 0.

F. Gross Necropsy

Each animal was euthanized by an intravenous injection of sodium pentobarbital following its final scoring interval. Gross necropsy examinations were not required for these animals.

G. Protocol Deviations

No protocol deviations occurred during this study.

IV. ANALYSIS OF DATA

The data for each animal was individually analyzed and summarized based on the Elf Atochem definitions presented below:

1. Nonirritant - Any test site that does not exhibit signs of dermal irritation (ex., no erythema and/or edema) following application of the test article.

2. Irritant - Any test site that exhibits reversible changes (ex., erythema and/or edema) following application of the test article.

3. Corrosive - Any test site that exhibits irreversible changes (ex., necrosis, ulceration, eschar) following application of the test substance.

V. MAINTENANCE OF RAW DATA AND RECORDS

All original paper data, the final report and magnetically encoded records were transferred to the SLI archives for a period of 10 years. The Sponsor will be contacted prior to final disposition of these items.

VI. RESULTS

A. Dermal Observations:

Individual Data: Table 1

Exposure to the test article produced moderate edema and moderate to severe blanching on 6/6 test sites at the 1 hour scoring interval. Additional dermal findings of eschar exfoliation and desquamation which were noted on 4/6 and 5/6 test sites, respectively and apparent necrosis and eschar which were noted on 6/6 test sites. The dermal irritation resolved completely in 1/6 animals by study day 14.

VII. CONCLUSION

Under the conditions of this test, Succinic Acid Peroxide is considered to be a corrosive to the skin of the rabbit.

Deborah A. Douds, M.S.
Study Director

Date 8/29/96

VIII. REPORT REVIEW

Todd N. Merriman, B.S., LATG
Toxicologist

Date 8/29/96

Kimberly L. Bonnette, M.S., LATG
Manager of Acute Toxicology

Date 8/29/96

IX. REFERENCES

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.

2. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

SLI STUDY NO.: 3255.101
CLIENT: ELF ATOCHEM

TABLE 1
A PRIMARY SKIN IRRITATION STUDY IN RABBITS
INDIVIDUAL DERMAL IRRITATION SCORES

Animal No./Sex Body Weight (kg)	Scoring Interval	Erythema	Edema	Comments[a]
3947/M	1 Hour	M-4	3	BLA-4, NEC-2 (LB)
2.492	24 Hours	M-4	2	BLA-4, ES-2
	48 Hours	M-4	2	BLA-1, ES-2
	72 Hours	M-4	2	BLA-1, ES-3
	7 Days	2	0	ES-1, EXF
	10 Days	2	0	
	14 Days	0	0	
3949/M	1 Hour	M-4	3	BLA-4, NEC-2(LB)
2.406	24 Hours	M-4	3	BLA-4, NEC-2 (LB), ES-1, DES
	48 Hours	M-4	3	BLA-4, ES-3[b]
	72 Hours	M-4	3	BLA-4, ES-4
	7 Days	M-4	3	ES-2, EXF, DES
	10 Days	M-4	2	ES-2, DES
	14 Days	2	1	
3951/M	1 Hour	M-4	3	BLA-4, NEC-2 (LB)
2.525	24 Hours	M-4	4	BLA-4, ES-3, ERB
	48 Hours	M-4	3	BLA-4, ES-3[b]
	72 Hours	M-4	3	BLA-4, ES-4
	7 Days	M-4	2	ES-2, EXF, DES
	10 Days	M-4	1	ES-2, DES
	14 Days	2	1	DES

[a]See Protocol Appendix A for definition of codes.
[b]Areas of the eschar appeared to be areas of previous apparent ulceration; however the areas were not moist.

NOTE: NEC-2 = Apparent necrosis >focal/pinpoint <25% of test site, LB = Light brown, ERB = Erythema extends beyond test site.

SLI STUDY NO.: 3255.101
CLIENT: ELF ATOCHEM

TABLE 1
A PRIMARY SKIN IRRITATION STUDY IN RABBITS
INDIVIDUAL DERMAL IRRITATION SCORES

Animal No./Sex Body Weight (kg)	Scoring Interval	Erythema	Edema	Comments[a]
3953/M	1 Hour	M-4	3	BLA-3, NEC-3 (LB)
2.420	24 Hours	M-4	3	BLA-4, NEC-1 (LB), ES-2
	48 Hours	M-4	3	BLA-4, ES-3
	72 Hours	M-4	2	BLA-4, ES-4
	7 Days	2	2	ES-1, DES
	10 Days	2	1	DES
	14 Days	1	1	
3955/M	1 Hour	M-4	3	BLA-4, NEC-2 (LB)
2.384	24 Hours	M-4	3	BLA-3, ES-3
	48 Hours	M-4	2	BLA-3, ES-3[b]
	72 Hours	M-4	2	BLA-4, ES-4
	7 Days	M-4	3	ES-2, DES
	10 Days	M-4	1	ES-2, DES
	14 Days	1	1	
3956/M	1 Hour	M-4	3	BLA-4, NEC-1 (LB)
2.468	24 Hours	M-4	4	BLA-3, ES-3
	48 Hours	M-4	3	BLA-2, ES-3[b]
	72 Hours	M-4	2	BLA-3, ES-4
	7 Days	M-4	2	ES-2, EXF, DES
	10 Days	2	1	DES
	14 Days	1	0	

[a]See Protocol Appendix A for definition of codes.
[b]Areas of the eschar appeared to be areas of previous apparent ulceration; however the areas were not moist.

NOTE: NEC-1 = Apparent necrosis focal and/or pinpoint areas in test site, NEC-2 = Apparent necrosis >focal/pinpoint <25% of test site, NEC-3 = Apparent necrosis >25% <50% of test site, LB = Light brown

APPENDIX A

Protocol

A PRIMARY SKIN IRRITATION STUDY IN RABBITS WITH SUCCINIC ACID PEROXIDE

PROTOCOL

Springborn Study No. 3255.101

Protocol No.: ELFATO/PSI-1
Issue Date: February 1996

Springborn Laboratories, Inc. (SLI)
Health and Environmental Sciences
640 North Elizabeth Street
Spencerville, Ohio 45887

Deborah A. Douds, M.S.
Study Director

For

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103

TABLE OF CONTENTS

I. PURPOSE

The purpose of this study is to assess the potential irritant and/or corrosive effects of a test article in rabbits when administered by a single dermal dose. This study is intended to provide information on the potential health hazards of the test article with respect to dermal exposure. Data from this study may serve as a basis for classification and/or labeling of the test article.

II. RESPONSIBILITIES

A. Sponsor

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103

B. Sponsor's Representative

Roy Bannister, Ph.D.
Phone: (215) 419-5875
FAX: (215) 419-5800

C. Testing Location

Springborn Laboratories, Inc.
Health and Environmental Sciences
553 North Broadway
Spencerville, OH 45887
Phone: (419) 647-4196
FAX: (419) 647-6560

D. Personnel Responsibilities

1. Deborah A. Douds, M.S.
   Study Director/Toxicologist

2. Kimberly L. Bonnette, M.S., LATG
   Alternate Contact/Manager of Acute Toxicology

3. Todd N. Merriman, B.S., LATG
   Toxicologist

4. Robert B. Foster
   President and Managing Director

5. Malcolm Blair, Ph.D.
   Director of Research

6. Rusty E. Rush, M.S., LAT, DABT
   Associate Director of Toxicology

7. J. Dale Thurman, D.V.M, M.S., DACVP
   Director of Pathology

8. Elaine Daniel, Ph.D., DABT
   Associate Director of Toxicology

9. Anita M. Bosau
   Director of Compliance Assurance

III. PROPOSED STUDY SCHEDULE

A. Initiation of In-Life Phase: June, 1996

B. Completion of In-Life Phase: July, 1996

C. Audited Report Date: 4 Weeks Following Sponsor's Approval for Study Termination

IV. TEST ARTICLE IDENTIFICATION

A. Test Article

1. Sponsor's Identification

Succinic Acid Peroxide

2. SLI Test Article Identification Number

S96.012.3255

3. Characteristics

The Sponsor is responsible for any necessary evaluations related to identity, strength, purity, composition, stability and method of synthesis of the test material according to 21 CFR 58.105, and 40 CFR 792.105. Any special storage conditions for the test article will be supplied by the Sponsor.

4. Handling Precautions

Safety data regarding the test article should be provided by the Sponsor [Material Safety Data Sheet (MSDS) or equivalent, if available]. Technical personnel are required to read this information prior to handling the test article. Any question concerning this information should be referred to the Study Director.

Additional safety and handling information may be provided by the Study Director and/or Sponsor. Minimum safety requirements include safety glasses, impervious gloves, and laboratory wear. An MSDS shall also be available for any chemical entities utilized in the conduct of this study.

B. Retention Sample

Where necessary, the Sponsor will be responsible for maintaining a retention sample of the test article.

C. Test Article Disposition

The test article will be returned to the Sponsor following completion of all studies with the test article(s) unless otherwise instructed by the Sponsor.

D. Method of Test Article Preparation

Liquids, gels and pastes are generally administered as received from the Sponsor. Solids and powders are also generally dosed as received from the Sponsor and will be moistened with 0.5 mL of distilled water or, where necessary, a suitable vehicle to enhance test article contact with the skin. Solids and powders may need to be ground and sieved prior to test use in order to reduce particulate size and to improve homogeneity. The test article will be prepared and/or dispensed fresh on the day of dosing. The method of preparation will be documented in the raw data and presented in the final report.

V. TEST SYSTEM

A. Justification of the Test System

1. The rabbit is the preferred species for primary skin irritation testing by various U.S. and International regulatory agencies.

2. The New Zealand White rabbit has been shown to be sensitive to the irritant/corrosive effects of a variety of drugs and chemicals. Therefore, this species and strain is a reasonable alternative to larger mammals for primary skin irritation testing of drugs and chemicals for human safety assessment.

3. The New Zealand White rabbit has been used extensively for skin irritation testing. Thus, data from this study may be compared and contrasted to other studies performed in New Zealand White rabbits.

4. Historical information concerning New Zealand White rabbits is available at SLI and in the published literature.

5. Healthy, outbred New Zealand White rabbits may be obtained from reliable, USDA approved and regulated suppliers.

6. The laboratory rabbit may be safely handled and manipulated by trained technical personnel.

SLI has conducted literature searches through Medline, Toxline and Bioethics and there are no generally accepted validated alternatives to this test. In a 1989 position paper prepared by the Animals in Research Committee of The Society of Toxicology (SOT) and approved by the SOT Council, it was concluded that "none of these proposed models are yet validated or evaluated for a broad range of chemical moieties, and none can be relied upon to provide the scientific reliability or predictive accuracy which would be required for a new test for regulatory of legal acceptability" [1].

B. Justification of the Route of Exposure and Number of Animals

1. Dermal administration of the test substance was selected since this is a potential route of human exposure.

2. Since New Zealand White rabbits have no pigment and have a relatively large dorsal surface area, dermally administered substances may be accurately applied and any resulting effects easily observed.

3. The number of animals used on this study will be consistent with the guidelines published by a number of U.S. and International regulatory agencies including EPA-FIFRA, EPA-TSCA, FDA, CPSC-FHSA, DOT, IMO, EEC, OECD, MAFF and MOHW.

C. Description

1. Species

Rabbit

2. Strain

New Zealand White

3. Source

Myrtle's Rabbitry or another USDA approved supplier

4. Age and Body Weight Range

   Adult, approximately 2.0 to 3.5 kg (prior to dosing on day 0).

5. Number of Animals/Sex on Study

   6 rabbit test (males and/or females)

D. Method of Identification

Plastic ear tags displaying unique identification numbers will be used to individually identify the animals. The cage cards will display at least the study number, animal number, and sex and will be affixed to each cage.

E. Animal Husbandry

1. Housing

   The animals will be housed individually in suspended stainless steel cages. All housing and care will be based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [2].

2. Environment

   The environmental conditions for the animal room will be set to maintain room temperature and relative humidity ranges of 67 ± 6°F and 55 ± 15%, respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers will be set to maintain a 12-hour light/12-hour dark cycle and the room ventilation will be set to produce 10-15 air changes/hour. The room temperature and relative humidity will be recorded a minimum of once daily.

3. Food

   PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.) will be provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study will be recorded. The feed is analyzed and certified by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin

are set by the manufacturer. Within these limits, there are no contaminants reasonably expected in the diet which would interfere with the conduct of the study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained in the laboratory records. Feed that is outside the ranges set for the above mentioned criteria will not be utilized by the testing facility.

4. Water

Municipal tap water following treatment by reverse osmosis will be available ad libitum throughout the study. The purified water will be supplied by an automatic watering system. Monitoring of the drinking water for contaminants will be conducted annually by the testing laboratory and the records will be available for inspection. Levels of contaminants which may be present are not expected to compromise the purpose of the study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR, Part 141).

F. Acclimation

Upon receipt, the animals will be removed randomly from the shipping cartons, examined by qualified personnel, identified with plastic ear tags, and then acclimated to the laboratory conditions for a minimum of 5 days. The animals will be observed daily for overt physical or behavioral abnormalities, general health/moribundity and mortality.

G. Animal Selection

The animals chosen for study use will be arbitrarily selected from healthy stock animals to avoid potential bias. All animals will receive a detailed pretest observation prior to dosing. Only healthy animals will be chosen for study use. Females will be nulliparous and nonpregnant.

VI. EXPERIMENTAL DESIGN AND PROCEDURES

A. Study Group Design

A six rabbit test will be performed. Materials which are determined by the Sponsor to be strong acids (pH ≤ 2.0), strong alkalis (pH ≥ 11.5) or highly toxic by the dermal route (LD50 <200 mg/kg) need not be tested in a full number of animals due to their predictive corrosive or toxic properties. However, at the request of the Sponsor, these materials will be administered to one animal. If no severe response (i.e., corrosion and/or death) is seen during the first 72 hours, the material will be tested on the remaining five animals.

B. Preliminary Procedures

On day -1, the animals chosen for use on the primary skin irritation study will have the fur removed from the dorsal area of the trunk using an animal clipper. Care will be taken to avoid abrading the skin during the clipping procedure.

C. Dosing

On the following day (day 0), the test article will be applied to a small area of intact skin on each test animal (approximately 1 inch x 1 inch) as indicated below:

1. If the test article is a liquid, gel or paste, a 0.5 mL dose of the material will be administered under an approximate 1 inch x 1 inch square 4-ply gauze patch. The gauze patch will be held in contact with the skin at the cut edges with a non-irritating tape. Removal and ingestion of the test article will be prevented by placing an elastic wrap over the trunk and test area (semi-occlusive binding). The elastic wrap will then be further secured with adhesive tape around the trunk at the cranial and caudal ends.

2. If the test article is a solid or a powder, 0.5 g of the test article will be applied to an approximate 1 inch x 1 inch square 4-ply gauze patch. The test article will then be moistened with 0.5 mL of distilled water and the gauze patch applied to the test site. The gauze patch will be held in contact with the skin at the cut edges with a non-irritating tape. Removal and ingestion of the test article will be prevented by placing an elastic wrap over the trunk and test area (semi-occlusive binding). The elastic wrap will then be further secured with adhesive tape around the trunk at the cranial and caudal ends.

Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If such is noted, the Sponsor will be contacted to see if the animals should be humanely euthanized. After dosing, collars will be placed on each animal and will remain in place until removal on day 3. After a four-hour exposure period, the elastic wrap and gauze patch will be removed from each animal and the corners of the test site delineated using a marker. Residual test article will be removed using gauze moistened with distilled water followed by dry gauze. If the distilled water does not sufficiently remove the test article residue, the Study Director/Sponsor may choose to use another appropriate solvent.

D. Body Weights

Individual body weights will be obtained for each animal prior to dosing on day 0.

E. Dermal Observations

Animals will be examined for signs of erythema and edema and the responses scored at approximately 1, 24, 48 and 72 hours after patch removal according to the Macroscopic Dermal Grading System presented in Protocol Appendix A which is based on Draize [3]. If there is no evidence of dermal irritation at the 72 hour scoring interval, the study will be terminated. If dermal irritation persists at any test site, the observation period may be extended for the affected animals (scored on days 7, 10 and 14). Animals requiring an extended observation period will remain on test (up to and including 14 days post-dose) until the irritation has resolved, permanent injury is evident, or the Study Director/Sponsor determines that additional scoring intervals are unnecessary. The dermal test sites may be reclipped as necessary to allow clear visualization of the skin.

F. Clinical Observations

Any unusual observations and/or mortality will be recorded. General health/mortality checks will be performed in the morning and in the afternoon.

G. Unscheduled Deaths and Euthanasia

Any animals dying or euthanized for cause during the study period will be necropsied. The animals will be euthanized by an intravenous injection of sodium pentobarbital. Body cavities (cranial, thoracic, abdominal and pelvic) will be opened and examined. No tissues will be retained.

H. Scheduled Euthanasia

Each surviving animal will be euthanized by an intravenous injection of sodium pentobarbital following each animal's final scoring interval. A gross necropsy examination will not be required for surviving animals.

VII. PROTOCOL AMENDMENT

Alterations to this protocol may be made as the study progresses. No changes in the protocol will be made without the specific consent of the Sponsor's Representative. A protocol amendment will be prepared and signed by the Study Director, SLI Quality Assurance and Sponsor's Representative for any such changes.

VIII. DATA REPORTING

One unbound copy of the draft report (if requested) and two copies of the final report (one bound and one unbound) will be submitted to the Sponsor. The final report will include all information necessary to provide a complete and accurate description and evaluation of the experimental procedures and results.

The report will include at least the following information and data:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References

- Data Tables
- Protocol and Amendments
- SLI Personnel Responsibilities

IX. ANALYSIS OF DATA

The data for each animal will be individually analyzed and summarized in the report based on the Elf Atochem definitions presented below:

1. Non Irritant - Any test site that does not exhibit signs of dermal irritation (ex., no erythema and/or edema) following application of the test article.

2. Irritant - Any test site that exhibits reversible changes (ex., erythema and/or edema) following application of the test article.

3. Corrosive - Any test site that exhibits disintegration or irreversible alteration at the site of contact. Eschar may be defined as corrosion provided that the integrity of the dermis is altered. Corrosion is generally manifested by ulceration and necrosis with subsequent scar tissue formation. Erythema, edema, subcutaneous hemorrhage, fissuring and atonia are not considered evidence of corrosion.

X. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

All original data, magnetically encoded records, specimens and reports from this study are the property of the Sponsor. These materials shall be available at SLI to facilitate auditing of the study during its progress and prior to acceptance of the final report. All original paper data, the final report, magnetically encoded records, and any specimens will be transferred to the SLI archives for a period of 10 years. The Sponsor will be contacted prior to the final disposition of these items.

XI. REGULATORY COMPLIANCE

This study may be submitted to and will be conducted in accordance with EPA-TSCA [4], OECD [5] and EEC [6] guidelines and the principles of the Good Laboratory Practice regulations by the FDA (21 CFR Part 58), the EPA (40 CFR Part 792) and the OECD [Annex 2 C(81)30].

XII. QUALITY ASSURANCE

The study will be inspected at least once during the in-life phase by the Springborn Laboratories, Inc., Quality Assurance Unit to assure compliance with Good Laboratory Practice regulations, SLI's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The final report will be audited prior to submission to the Sponsor to ensure that it completely and accurately describes the test procedures and results of the study.

XIII. USDA ANIMAL WELFARE COMPLIANCE STATEMENT

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress and pain to animals. All methods are described in this study protocol or in written laboratory standard operating procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management. Methods of euthanasia used during the study are in conformance with the above referenced regulations and the American Veterinary Medical Association Panel on Euthanasia [7]. This protocol has been reviewed and approved by Springborn Laboratories, Inc. Institutional Animal Care and Use Committee (IACUC) for a maximum of 12 animals. Prior IACUC approval will be obtained for repeated studies.

This study is being conducted to evaluate the potential irritant effects of the test article and potential reversibility of such effects. Following dosing, the Study Director will be notified by the technician if severe local reactions occur, if the animals exhibit overt clinical indications of pain/distress post-dose or if delayed severe dermal or clinical changes subsequently develop. If severe responses are noted, the Study Director will contact the Facility Veterinarian and Sponsor to consider an appropriate course of action. In the event that the Sponsor cannot be contacted, the Study Director and/or Facility Veterinarian may authorize treatment or euthanasia of the animals. In general, the dermal tissue will not be anesthetized prior to or following dosing since the anesthetic may influence dermal penetration of the test article which may alter the irritation response. Furthermore, anesthetic agents may interact with and/or dilute the test article and thereby alter the experimental results. However, if it is suspected that the test article may induce more than transient pain/distress based on existing information, preanesthesia will be considered. In such circumstances, the Study Director and/or Facility Veterinarian will consult with the Sponsor to devise an appropriate study plan.

XIV. DECLARATION OF INTENT

This study will be listed on the SLI Quality Assurance Master Schedule for the EPA.

XV. GENERIC PROTOCOL APPROVAL

The Sponsor's signature below documents that there are no acceptable non-animal alternatives for this study, and that since this study is required by the relevant supervising government agency, it does not unnecessarily duplicate any previous experiments.

Kimberly L. Bonnette, M.S., LATG
Manager of Acute Toxicology

Date: 3/20/96

Quality Assurance Unit (SLI)

Date: 3/20/96

Roy Bannister, Ph.D.
Sponsor's Representative
(Principal Investigator)

Date: 3/22/96

XVI. STUDY SPECIFIC PROTOCOL APPROVAL

Deborah A. Douds, M.S.
Study Director (SLI)

Date: 6/4/96

Quality Assurance Unit (SLI)

Date: 6/4/96

XVII. REFERENCES

1. SOT Position Paper, "Comments on the LD50 and Acute Eye and Skin Irritation tests," Fundamental and Applied Toxicology 13, 621-623, 1989.

2. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.

3. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

4. Toxic Substances Control Act Test Guidelines, 40 CFR Part 798, Subpart E, Section 798.4470, July 1, 1992.

5. OECD Guidelines for the Testing of Chemicals, Section 4, Health Effects, Subsection 404, July 17, 1992.

6. The EEC Guidelines Part B: Methods for the Determination of Toxicity, No. L 383 A/124, B.4, December 29, 1992.

7. 1993 Report of the American Veterinary Medical Assoc. Panel on Euthanasia, JAVMA, Vol. 202, No. 2, pp. 229-249, January 15, 1993.

PROTOCOL APPENDIX A

Macroscopic Dermal Grading System

Erythema and Edema Observations		
Observation	Definition	Code
Erythema - Grade 0	No erythema	0
Erythema - Grade 1	Very slight erythema (barely perceptible)	1
Erythema - Grade 2	Well-defined erythema	2
Erythema - Grade 3	Moderate to severe erythema	3
Erythema - Grade 4	Severe erythema (beet redness)	4
Maximized Grade 4	Injuries in depth (see below)	M - 4 (see below)
Edema - Grade 0	No edema	0
Edema - Grade 1	Very slight edema (barely perceptible)	1
Edema - Grade 2	Slight edema (edges of area well defined by definite raising)	2
Edema - Grade 3	Moderate edema (raised approximately 1 millimeter)	3
Edema - Grade 4	Severe edema (raised more than 1 millimeter and extends beyond the area of exposure)	4

NOTE: Each animal is assigned an erythema and edema score. The most severely affected area within the test site is graded. If eschar, blanching and/or ulceration that is greater than focal/pinpoint is observed, then the "Maximized Grade 4" is assigned to the test site in place of the erythema score and the type of injuries in depth (e.g., eschar - mild, blanching - moderate, ulceration - severe, etc.) will be noted. The presence of any other dermal changes (e.g., desquamation, fissuring, eschar exfoliation, etc.) will also be recorded.

PROTOCOL APPENDIX A

Macroscopic Dermal Grading System

Eschar, Blanching and Ulceration Observations		
Observation	Definition	Code
Eschar - Focal/Pinpoint	Focal and/or pinpoint areas in test site	ES - 1
Eschar - Mild	>focal/pinpoint <25% of test site	ES - 2
Eschar - Moderate	>25% <50% of test site	ES - 3
Eschar - Severe	>50% of test site	ES - 4
Blanching - Focal/Pinpoint	Focal and/or pinpoint areas in test site	BLA - 1
Blanching - Mild	>focal/pinpoint <25% of test site	BLA - 2
Blanching - Moderate	>25% <50% of test site	BLA - 3
Blanching - Severe	>50% of test site	BLA - 4
Ulceration - Focal/Pinpoint	Focal and/or pinpoint areas in test site	U - 1
Ulceration - Mild	>focal/pinpoint <25% of test site	U - 2
Ulceration - Moderate	>25% <50% of test site	U - 3
Ulceration - Severe	>50% of test site	U - 4

Additional Dermal Observations		
Observation	Definition	Code
Desquamation	Characterized by scaling or flaking of dermal tissue with or without denuded areas. Scab-like or slough-like areas of eschar are not scored for desquamation.	DES
Fissuring	Characterized by cracking of the skin or eschar formation (slough and/or scab) that is associated with moist exudate. Fissuring should be checked prior to manipulating the test site.	FIS
Eschar Exfoliation	The process by which a scab-like or slough-like formation flakes off the test site.	EXF
Test Site Staining	Skin located at the test site appears to be stained/discolored (note color of staining).	TSS

Any additional dermal findings will be noted in the raw data and included in the final report.

APPENDIX B

Individual Clinical Observations

A PRIMARY SKIN IRRITATION STUDY IN RABBITS
INDIVIDUAL CLINICAL OBSERVATIONS
(POSITIVE FINDINGS)

Group	Animal No./Sex	Clinical Observation
Intact	3947/M	Apparent mechanical injury - right hindlimb; 1 hour
	3953/M	Collar caught in mouth - removed; day 0 Dark material around mouth; days 0,1, 2, 3, 4 Swollen mouth area; day 1
	3955/M	Decreased defecation; day 3 Low food consumption; day 3

APPENDIX C

SLI Personnel Responsibilities

SLI PERSONNEL RESPONSIBILITIES

Deborah A. Douds, M.S.	Study Director/Toxicologist
Kimberly L. Bonnette, M.S., LATG	Alternate Contact/Manager of Acute Toxicology
Robert B. Foster	President and Managing Director
Malcolm Blair, Ph.D.	Director of Research
Rusty E. Rush, M.S., LAT, DABT	Associate Director of Toxicology
Todd N. Merriman, B.S., LATG	Toxicologist
Patricia K. Jenkins, A.A.S., LATG, RILAM	Supervisor of Acute Toxicology
Pamela S. Smith, ALAT	Unit Leader
Delores P. Knippen	Supervisor of Pharmacy
Jan K. Severt, B.S., ALAT	Supervisor of Acute Report Preparation
Anita M. Bosau	Director of Compliance Assurance
J. Dale Thurman, D.V.M., M.S. DACVP	Director of Pathology